JACC Vol. 20, No. 6
November 15, 1992:1326–32

# Relation Between Ventilation and Carbon Dioxide Production in Patients With Chronic Heart Failure

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***Objectives.*** **The aim of this study was to analyze the relation between ventilation and carbon dioxide production and the control of ventilation in patients with chronic heart failure.**

***Background.*** **Patients with chronic heart failure exhibit an increased ventilatory response to exercise. Ventilation is closely linked to carbon dioxide production, producing a high correlation between the two variables. This relation is nonlinear at high levels of exercise.**

***Methods.*** **The ventilation/carbon dioxide production ratio during exercise was examined in 29 patients with chronic heart failure and 9 normal volunteers.**

***Results.*** **In the patients with heart failure, there were three patterns: in the least severely affected patients, the pattern was similar to that of the normal subjects, with an initial decrease in the ventilation/carbon dioxide production ratio to a plateau maintained during exercise; in more severely affected patients, there was an increase in the ratio at the end of exercise, and in the most severely affected patients, the ratio increased from the outset of exercise. The ventilation/carbon dioxide relation is not adequately described by a straight line relation.**

***Conclusions.*** **The ventilation/carbon dioxide ratio is not fixed, and the changes that occur in this ratio reflect either a noncarbon dioxide-driven ventilatory stimulus or an increase in ventilation-perfusion mismatch due to increased dead space ventilation. The different patterns of this ratio may provide clues to the pathophysiologic mechanisms of the excessive ventilation and breathlessness seen during exercise in chronic heart failure.**

***(J Am Coll Cardiol 1992;20:1326–32)***

Patients with chronic heart failure suffer from tiredness and breathlessness on exercise, but the cause of the breathlessness remains unclear. It is well recognized that on formal testing, such patients have an increased ventilatory response to exercise (1–4). To find improved treatment for this symptom will require a better understanding of the abnormalities of respiration in heart failure. It is not known, for example, whether the increased ventilation is due to altered ventilation-perfusion matching in the lungs or to altered control of ventilation; yet, the therapeutic correction of these abnormalities may require different strategies.

In common with normal subjects, patients with heart failure retain near normal arterial blood gases on exercise (5,6), and ventilation continues to be closely tied to carbon dioxide production (3,7,8); for any given rate of carbon dioxide production in these patients, ventilation is increased as is the ventilatory response to any given work load (9). Thus, the slope of the relation of ventilation to carbon dioxide production is increased.

From the Department of Cardiac Medicine, National Heart and Lung Institute, London, England. Dr. Clark is supported by the Robert Luff Foundation, London; and Dr. Coats is supported by the Viscount Royston Trust and the British Heart Foundation, London.

Manuscript received February 24, 1992; revised manuscript received May 23, 1992, accepted May 29, 1992.

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However, closer examination of the ventilation/carbon dioxide production ratio slope, reveals that although this relation appears almost linear, at the onset of exercise there is an initial decline in the "instantaneous" value of ventilation/carbon dioxide production ratio that is followed by a plateau phase during steady state exercise. There is also an increase in slope toward the end of exercise (3). Thus, although a high degree of correlation is seen, the relation of ventilation to carbon dioxide production is not linear. To examine the possible changes in ventilatory efficiency in chronic heart failure, we examined this relation during treadmill exercise in 9 normal subjects and 29 patients with chronic heart failure.

## Methods

Approval for this study was granted by the Ethics Committee of the Royal Brompton National Heart and Lung Hospital, London.

**Normal subjects.** Nine healthy volunteers (eight men and one woman with a mean age of 29.9 years [range 25 to 35]) who were nonsmokers with no past history of cardiopulmonary disease exercised for 5 min at stage 1 followed by stages 3 and 5 and as much as possible of stage 7 of a standard Bruce protocol. Minute ventilation, oxygen consumption and carbon dioxide production were determined by expired gas analysis with a mass spectrometer (Airspec) with use of a standard argon-dilution method (10,11). Expired air was



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sampled at intervals of 10 s. From these data, maximal oxygen consumption and respiratory exchange ratio were calculated. The ventilatory equivalent for carbon dioxide was plotted against time. For analysis, the ventilatory equivalents were averaged for each stage of exercise.

**Patients.** Twenty-nine patients (25 men and 4 women with a mean age of 52.3 years [range 23 to 72]) with a diagnosis of chronic heart failure took part in the study. Seventeen patients had ischemic heart disease and 12 had dilated cardiomyopathy. All patients had had symptoms for >6 months before the study. All were using diuretic agents (average dose equivalent to approximately 70 mg of furosemide), and 15 were taking an angiotensin-converting enzyme inhibitor.

Patients undertook symptom-limited exercise with the use of a Bruce treadmill protocol, modified by the addition of a "stage 0" (equivalent to stage 1 with no elevation) for 3 min at the start of exercise. There was no history or X-ray evidence of pulmonary disease. The same expired air data obtained for the normal subjects were acquired.

In a subset of patients, arterial blood samples were collected from a radial arterial line inserted under local anesthesia into the right or left brachial artery. Arterial blood was collected at rest, during submaximal exercise and at peak exercise. Blood was immediately analyzed using a Ciba-Corning 278 Blood Gas System after a 2-point calibration, for arterial carbon dioxide and oxygen tensions.

**Analysis.** Ventilation and carbon dioxide production were determined in liters/min; hence, the ventilation/carbon dioxide production ratio is dimensionless. To correct for different exercise times, we divided exercise data into consecutive 2-min segments and compared ventilation/carbon dioxide production ratio values among patients at rest and at the start, middle and end of exercise.

In normal subjects, we estimated anatomic dead space ventilation by calculating anatomic dead space from a standard formula (12) and multiplying by respiratory rate.

We first observed the plot of ventilation/carbon dioxide production ratio versus exercise time in normal subjects and found it to be an L-shaped curve (see Results). We classified the patients with heart failure into three groups on the basis of the visual appearance of this plot. In Group 1 the plot was an L-shaped curve similar in appearance to that of the normal subjects. In Group 2 the plot was a U-shaped curve with a marked increase in ventilation/carbon dioxide production ratio toward the end of exercise after an initial decrease at the onset. In Group 3 the plot exhibited a constant increase in ventilation/carbon dioxide production ratio during exercise. The groups were determined by two of us on two occasions without knowledge of the patient characteristics or the results obtained by the other observer. On all four occasions, patients were assigned to the same categories.

Patients in Group 1 were defined as having a value for ventilation/carbon dioxide production ratio at peak exercise within 10% of the value for the preceding 2 min. Group 2 patients were defined as having an initial decrease in this ratio with an increase at the end of exercise to a value within ≥10% of that at the onset of exercise. In Group 3 patients, there was no initial decrease in the ratio but an increase over the period of exercise.

Data from blood gas analysis were used to estimate physiologic dead space by using the Bohr equation:

$$V_D/V_T = (P_{aCO_2} - P_{\bar{E}CO_2})/P_{aCO_2}, \quad [1]$$

where $V_D/V_T$ is physiologic dead space as a proportion of tidal volume, $P_{aCO_2}$ is the arterial carbon dioxide tension and $P_{\bar{E}CO_2}$ is mixed expired carbon dioxide.

**Statistical methods.** Between-group analysis was performed with the Student *t* test with corrections for multiple comparisons with the Scheffé procedure. Linear regression using the least squares method was used. p values < 0.05 were taken to be significant. Data are expressed as mean value ± SD.

**Table 1.** Data From Nine Normal Subjects

| Subject | $Vo_{2max}$ | $V_E/Vco_2$ | | | |
|---|---|---|---|---|---|
| | | Overall | Rest | 50% | Peak |
| A | 47.99 | 18.65 | 32.65 | 20.89 | 20.05 |
| B | 37.32 | 22.80 | 32.68 | 23.82 | 24.31 |
| C | 39.70 | 22.10 | 33.09 | 25.13 | 24.67 |
| D | 46.57 | 26.60 | 34.93 | 21.30 | 21.76 |
| E | 36.72 | 19.90 | 30.71 | 20.35 | 21.14 |
| F | 38.00 | 23.78 | 28.86 | 23.63 | 24.67 |
| G | 45.82 | 28.33 | 37.35 | 28.66 | 30.38 |
| H | 50.73 | 20.11 | 29.64 | 21.00 | 20.68 |
| I | 32.83 | 25.91 | 37.09 | 26.52 | 29.30 |
| Mean | 41.74 | 23.13 | 33.00 | 23.48* | 24.11 |
| SD | 6.15 | 3.32 | 3.03 | 2.88 | 3.67 |

*$p < 0.001$ versus values at rest. Rest, 50%, Peak and Overall = instantaneous $V_E/Vco_2$ values at rest, at 50% of eventual duration of exercise and at peak exercise and overall value, respectively; $V_E/Vco_2$ = gradient of plot of ventilation versus carbon dioxide production; $Vo_{2max}$ = maximal oxygen uptake (ml/min per kg).

## Results

**Normal subjects (Table 1).** A typical pattern of ventilation/carbon dioxide production ratio against time is shown in Figure 1. All subjects showed the same response with an initial decrease in ventilation/carbon dioxide production ratio (mean ± SD 33.0 ± 3.03 at rest and 25.51 ± 2.76 for stage 1 [not seen in table], $p < 0.001$). This ratio continued to decrease with a mean ventilation/carbon dioxide production ratio of 23.48 ± 2.88 at 50% of maximal exercise ($p < 0.001$ vs. stage 1). The average of the last 10 measurements before the test was stopped because of fatigue (24.12 ± 3.7, $p = 0.008$) was significantly *higher* than that for the preceding stage (that is, the last completed stage for each subject before the test was stopped). Thus an L-shaped relation between ventilation/carbon dioxide production ratio and exercise load was found in all nine normal subjects. This

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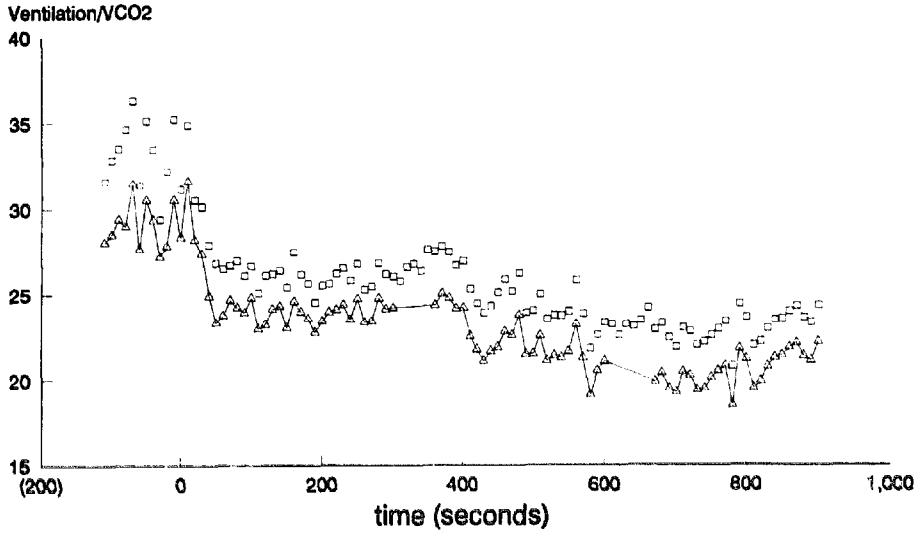


**Figure 1.** Ventilation/carbon dioxide production ratio (ventilation/$Vco_2$) (squares) plotted against time in a normal subject. The **triangles** indicate the *alveolar* ventilation/carbon dioxide production ratio, correcting for anatomic dead space ventilation. The points before zero represent rest data immediately before exercise.

pattern persisted after correction for anatomic dead space ventilation (Fig. 1).

**Patients.** *Group 1 (Table 2).* In this group of patients, a response was similar to that in normal subjects (Fig. 2), with an initial decrease in ventilation/carbon dioxide production ratio from rest to a plateau seen at 50% of subsequent maximal exercise (44.63 vs. 36.23, $p < 0.001$). There was a further small decline at peak exercise (36.23 vs. 35.13, $p < 0.001$). However, the initial, trough and final ventilation/carbon dioxide production ratio values were all significantly higher than those for normal subjects ($p < 0.001$ for each comparison).

*Group 2 (Table 3).* This group demonstrated a U-shaped response of ventilation/carbon dioxide production ratio over time during exercise (Fig. 2). There was an initial decline in the ratio (from 41.20 at rest to 36.59 at 50% of maximal exercise, $p < 0.05$) with a subsequent increase at the end of exercise (36.59 rising to 43.28, $p < 0.01$).

*Group 3 (Table 4).* In this group, we observed an increase in ventilation/carbon dioxide production ratio over time (Fig. 2). Individual linear correlation coefficients ranged from 0.52 to 0.85 (average 0.75); p values in each case were $<0.001$.

*Differences among Groups 1 to 3 (Table 5).* Group 1 patients had a higher average maximal oxygen consumption than that of the other two groups (16.04 ± 4.6 vs. 13.35 ± 3.3 ml/min per kg, $p < 0.01$). The exercise time was significantly longer in Group 1 than in Group 2 ($p < 0.05$) and longer in Group 2 than in Group 3 ($p < 0.01$), implying a worsening degree of heart failure across the three classes of ventilation/carbon dioxide production ratio response. There were no significant differences among patient groups in terms of etiology or current medication.

When the ratio of final to starting value for ventilation/carbon dioxide production ratio is determined, there is a highly significant linear correlation between this ratio and exercise time (Fig. 2) ($r = -0.66$, $p < 0.001$); that is, the greater the ratio (and the higher the peak ventilation/carbon dioxide production ratio relative to the rest value), the shorter the exercise time observed. Thus, there appears to be a significant correlation between the degree to which the ventilation/carbon dioxide production ratio increases during exercise and the severity of heart failure and the resulting limitation to exercise across the three groups of patients.

*Blood gas analysis (Table 6).* Data from blood gas analyses were available for nine patients (four in Group 1, two in Group 2 and three in Group 3). There were no significant changes in carbon dioxide or oxygen tensions during exercise and no differences among the groups. Calculated dead space fraction decreased significantly in all patients in whom it was measured (from a mean of 0.42 ± 0.06 at rest to 0.28

**Table 2.** Patients With Heart Failure: Group 1 (n = 14)

| Pt No. | $Vo_{2max}$ (ml/min per kg) | $Ve/Vco_2$ Overall | Rest | 50% | Peak | Ex Time (s) |
|---|---|---|---|---|---|---|
| 1 | 24.9 | 22.67 | 38.91 | 25.47 | 24.05 | 900 |
| 2 | 12.2 | 32.18 | 45.05 | 39.61 | 37.22 | 360 |
| 3 | 15.7 | 27.62 | 40.57 | 35.43 | 31.42 | 440 |
| 4 | 18.5 | 32.54 | 42.94 | 34.81 | 34.95 | 360 |
| 5 | 18.4 | 27.68 | 39.28 | 29.90 | 29.74 | 660 |
| 6 | 18.9 | 25.82 | 36.95 | 28.18 | 27.95 | 480 |
| 7 | 19.7 | 29.10 | 49.02 | 37.84 | 34.33 | 480 |
| 8 | 12.3 | 42.46 | 62.61 | 47.53 | 48.81 | 280 |
| 9 | 16.5 | 29.50 | 38.27 | 31.09 | 32.39 | 310 |
| 10 | 11.3 | 49.30 | 54.10 | 51.79 | 49.35 | 310 |
| 11 | 9.9 | 36.85 | 55.26 | 44.83 | 42.30 | 390 |
| 12 | 17.0 | 24.57 | 35.88 | 28.07 | 27.57 | 460 |
| 13 | 8.7 | 32.40 | 48.85 | 38.79 | 38.61 | 320 |
| 14 | 20.5 | 25.24 | 37.19 | 33.84 | 33.07 | 530 |
| Mean | 16.0 | 31.28 | 44 63 | 36.23* | 35.13 | 449 |
| SD | 4.6 | 7.36 | 8.20 | 7.80 | 7.6 | 166 |

*$p < 0.001$ versus values at rest. Ex Time = total duration of exercise time; Group 1 = patients with an L-shaped $Ve/Vco_2$ curve similar to that of normal subjects; Pt = Patient; other definitions as in Table 1.

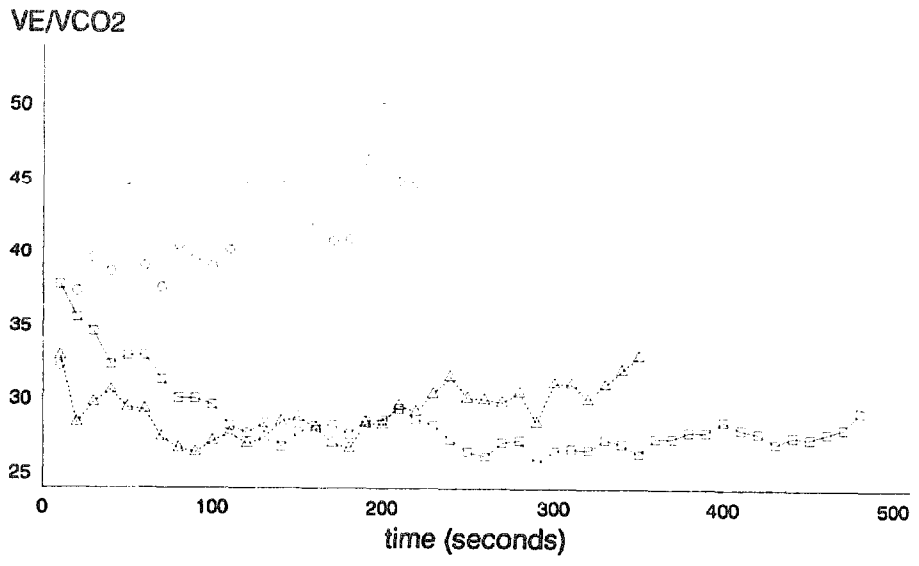


**Figure 2.** Ventilation/carbon dioxide production ratio ($V_E/V_{CO_2}$) against time in a patient from Group 1 (squares); Group 2 (triangles) and Group 3 (circles). See text for definitions of groups.

± 0.12 at peak exercise, p = 0.002). There were no observed differences in data among patients in different groups.

## Discussion

**Control of ventilation.** The relation between ventilation and carbon dioxide production is described by the equation derived by Whipp (4), a modification of the alveolar ventilation equation:

$$V_E = V_{CO_2} \times 863/P_{aCO_2} \times (1 - V_D/V_T), \quad [2]$$

where $V_D/V_T$ describes dead space ventilation as a proportion of tidal ventilation, $P_{aCO_2}$ is the arterial partial pressure of carbon dioxide and 863 is a constant to standardize gas measurements to body temperature, pressure and saturation. Thus, ventilation/carbon dioxide production ratio will vary with the arterial carbon dioxide and the dead space fraction; if the arterial partial pressure of carbon dioxide increases, then the ventilation/carbon dioxide production ratio will decrease; similarly, if dead space fraction increases, ventilation/carbon dioxide production ratio will increase.

In published data (7,8) from patients with heart failure, there appears to be a highly linear relation between ventilation and carbon dioxide production, with r values >0.9. However, if this relation were consistent, the plot of alveolar ventilation/carbon dioxide production ratio over time should approach a straight line parallel with the time axis. The plot of ventilation versus carbon dioxide production would asymptotically approach a straight line from a point above because of the decreasing proportion of total ventilation composed of anatomic dead space ventilation. This asymptotic curve for ventilation against carbon dioxide production was observed in our normal subjects and in our Group 1 patients (milder heart failure). It is the increase in ventilation/carbon dioxide production ratio toward the end of exercise that is abnormal, indicating a change in respiratory control.

**Changes in dead space on exercise.** Sullivan et al. (3) solved equation [2] for (1 − $V_D/V_T$) (that is, *non*-dead space fraction) to derive an estimate of dead space ventilation in

**Table 3.** Patients With Heart Failure: Group 2 (n = 8)

| Pt No. | $Vo_{2max}$ | $V_E/V_{CO_2}$ Overall | Rest | 50% | Peak | Ex Time |
|---|---|---|---|---|---|---|
| 15 | 14.4 | 34.91 | 43.85 | 38.73 | 40.54 | 370 |
| 16 | 13.5 | 33.25 | 36.40 | 32.41 | 35.73 | 280 |
| 17 | 17.6 | 38.64 | 35.47 | 32.38 | 37.27 | 390 |
| 18 | 17.5 | 63.30 | 41.21 | 39.61 | 62.88 | 490 |
| 19 | 10.6 | 41.77 | 55.35 | 38.26 | 40.78 | 270 |
| 20 | 13.4 | 73.31 | 45.61 | 43.52 | 56.00 | 300 |
| 21 | 17.8 | 30.59 | 32.45 | 28.68 | 31.46 | 350 |
| 22 | 11.7 | 41.91 | 39.22 | 39.12 | 41.55 | 270 |
| Mean | 14.6 | 44.71 | 41.20 | 36.59* | 43.28† | 340 |
| SD | 2.8 | 15.30 | 7.20 | 4.90 | 10.70 | 77 |

*p < 0.05 versus values at rest. †p < 0.01 versus value at 50% maximal exercise. Group 2 = patients with a U-shaped $V_E/V_{CO_2}$ curve with an initial decrease at the onset of exercise and a marked increase toward the end of exercise; other definitions as in Tables 1 and 2.

**Table 4.** Patients With Heart Failure: Group 3 (n = 7)

| Pt No. | $Vo_{2max}$ | $V_E/V_{CO_2}$ Overall | Rest | 50% | Peak | Ex Time (s) | $V/V_{CO_2}/t$ |
|---|---|---|---|---|---|---|---|
| 23 | 6.8 | 61.75 | 60.34 | 59.65 | 62.72 | 240 | 0.52 |
| 24 | 9.0 | 49.48 | 43.65 | 46.38 | 50.2 | 270 | 0.84 |
| 25 | 12.8 | 49.35 | 32.11 | 31.21 | 39.96 | 210 | 0.84 |
| 26 | 15.2 | 67.5 | 33.89 | 39.26 | 44.4 | 210 | 0.72 |
| 27 | 16.4 | 47.08 | 37.69 | 37.88 | 45.13 | 270 | 0.8 |
| 28 | 9.8 | 57.3 | 41.96 | 40.98 | 52.59 | 240 | 0.85 |
| 29 | 13.8 | 43.93 | 38.24 | 39.7 | 41.21 | 280 | 0.71 |
| Mean | 12 | 53.77 | 41.13 | 42.15 | 48.03 | 245 | 0.75 |
| SD | 3.5 | 8.60 | 9.40 | 8.90 | 7.90 | 29 | 0.1 |

Group 3 = patients with a constant increase in $V_E/V_{CO_2}$ during exercise; $V/V_{CO_2}/t$ = the slope of the relation between $V_E/V_{CO_2}$ and time during exercise; other definitions as in Tables 1 and 2.

**Table 5.** Comparisons Among Groups 1 to 3

| | Total Exercise Time (s) | | | $Vo_{2max}$ (ml/min per kg) | |
|---|---|---|---|---|---|
| | Group 1 (n = 14) | Group 2 (n = 8) | Group 3 (n = 7) | Group 1 (n = 14) | Groups 2 and 3 |
| | 900 (1) | 370 (15) | 210 (23) | 24.9 (1) | 14.4 (15) |
| | 360 (2) | 280 (16) | 210 (24) | 12.2 (2) | 13.5 (16) |
| | 440 (3) | 390 (17) | 270 (25) | 15.7 (3) | 17.6 (17) |
| | 360 (4) | 490 (18) | 240 (26) | 18.5 (4) | 17.5 (18) |
| | 660 (5) | 270 (19) | 280 (27) | 18.4 (5) | 10.6 (19) |
| | 480 (6) | 300 (20) | 240 (28) | 18.9 (6) | 13.4 (20) |
| | 480 (7) | 270 (21) | 270 (29) | 19.7 (7) | 9.0 (21) |
| | 280 (8) | 350 (22) | — | 12.3 (8) | 17.8 (22) |
| | 310 (9) | — | — | 16.5 (9) | 6.8 (23) |
| | 310 (10) | — | — | 11.3 (10) | 11.7 (24) |
| | 390 (11) | — | — | 9.9 (11) | 12.8 (25) |
| | 460 (12) | — | — | 17.0 (12) | 15.2 (26) |
| | 320 (13) | — | — | 8.7 (13) | 16.4 (27) |
| | 530 (14) | — | — | 20.5 (14) | 9.8 (28) |
| | | | | | 13.8 (29) |
| Mean | 448.6 | 340* | 245† | 16.04 | 13.35‡ |
| SD | 166.4 | 76.53 | 28.8 | 4.60 | 3.3 |

*$p < 0.05$ versus Group 1. †$p < 0.01$ versus Group 2. ‡$p < 0.01$ versus Group 1. Figures in parentheses indicate patient number. Abbreviations and definitions as in Tables 1 to 4.

patients with heart failure. In their study, as in ours, ventilation/carbon dioxide production ratio decreased in patients during exercise increasing at maximal exercise. These investigators also found that with exercise, dead space fraction decreased both in patients and in normal subjects but dead space *per breath* increased in patients; the maximal increase in dead space correlated with the maximal ventilation/carbon dioxide production ratio. They concluded that normal ventilatory control by carbon dioxide production occurs in heart failure and that the observed increase in ventilation was due to an increase in dead space ventilation.

**Table 6.** Blood Gas Analysis in Nine Patients*

| | Oxygen | | Carbon Dioxide | | $V_D/V_T$ | |
|---|---|---|---|---|---|---|
| | Rest | Peak | Rest | Peak | Rest | Peak |
| Mean | 12.77 | 12.83 | 4.99 | 4.92 | 0.42 | 0.28† |
| SD | 1.49 | 1.34 | 0.49 | 0.63 | 0.06 | 0.12 |

*Four patients from Group 1, two patients from Group 2 and three patients from Group 3. †$p = 0.002$ versus values at rest. Arterial tensions in kPal of oxygen and carbon dioxide at rest and at peak exercise. $V_D/V_T$ is calculated from equation 1 (see text) and represents the dead space fraction.

Their argument is circular, however. In their study, because dead space was calculated from ventilation/carbon dioxide production ratio, dead space and ventilation/carbon dioxide production ratio were highly correlated, and dead space was *forced* to be the likely abnormality producing increased ventilation.

Rajfer et al. (13), unlike Sullivan and coworkers (3), reported that patients with heart failure had a decrease in dead space fraction during exercise without an increase in this fraction at maximal exercise. In their study, dead space fraction was measured from the Bohr equation independent of ventilation/carbon dioxide production ratio. They concluded that during exercise, patients with heart failure show a decline in ventilation-perfusion mismatch even though they begin exercise with a larger dead space fraction than that of normal subjects. Similar conclusions were drawn from a study (14) using radionuclide ventilation–perfusion scans.

**Noncarbon dioxide stimuli to ventilation.** If a factor other than carbon dioxide production is driving ventilation, there should be a reduction in arterial carbon dioxide as a consequence of increased ventilation relative to carbon dioxide production. This reduction is seen in normal subjects at peak exercise (15,16). Hypocapnia is also seen in response to

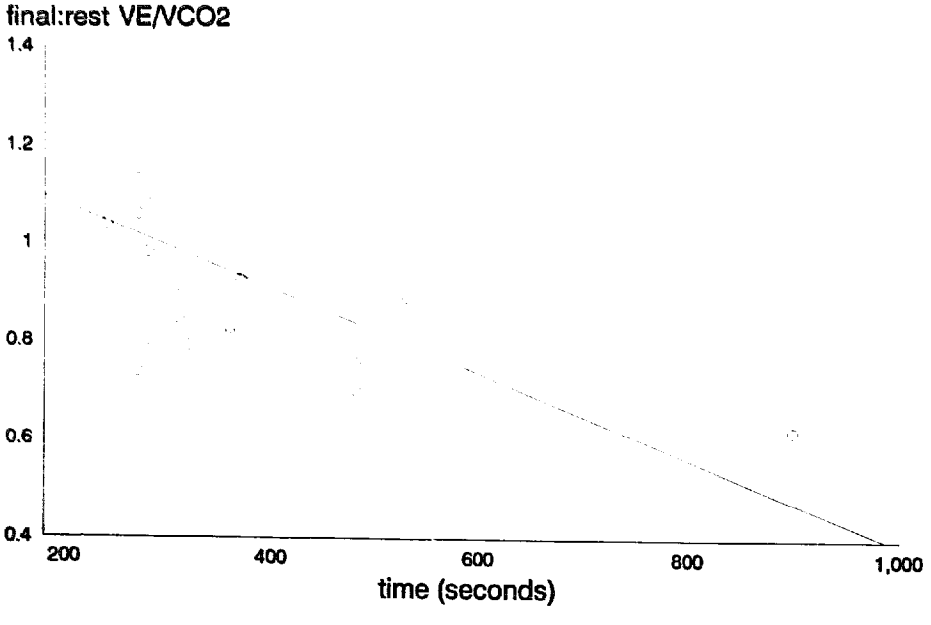


**Figure 3.** Ratio of final to rest value for ventilation/carbon dioxide production ratio ($VE/VCO_2$) plotted against duration of exercise in seconds.

*static* exercise (17) in normal subjects and is reported in patients with heart failure at peak exercise (3,13).

Attempts have been made to demonstrate a decoupling of ventilation from carbon dioxide production by using exercise regimens to deplete muscle glycogen (18,19), thus requiring exercising muscle to utilize a substrate other than glycogen. Under these conditions, carbon dioxide production should decrease and, if ventilation is coupled to carbon dioxide production, ventilation should also decrease. These results have *not* been found; thus, it may be that ventilation is decoupled from carbon dioxide production. However, in these experiments, dead space fraction and arterial carbon dioxide are assumed to remain constant, neither of which may be the case.

In a study that examined these variables directly, Caiozzo et al. (20) reported that arterial carbon dioxide was reduced after interventions to deplete glycogen. The increase in ventilation relative to carbon dioxide production subsequently seen was considered to reflect the ventilatory "cost" of maintaining a lower set point for arterial carbon dioxide. However, this increase may reflect a state in which another stimulus to breathing becomes predominant.

**Current findings.** Our normal subjects showed a decrease in ventilation/carbon dioxide production ratio at the onset of exercise until a plateau, was reached, followed by a small increase at the very end of exercise. The plateau phase represents the straight line relation between ventilation and carbon dioxide production. At the onset of exercise, the decrease in ventilation/carbon dioxide production ratio may reflect an increase in arterial carbon dioxide or a decrease in dead space fraction. This result may be due, at least in part, to changes in respiratory pattern causing a reduction of anatomic dead space ventilation. Similarly, the rise in ventilation/carbon dioxide production ratio at the end of exercise may represent an increase in the dead space/tidal volume ratio or another drive to ventilation resulting in a decrease in arterial carbon dioxide.

An examination of the ventilation/carbon dioxide production ratio pattern after correcting for the effects of changes in anatomic dead space ventilation shows that the pattern of an increase in respiratory "efficiency" at the onset of exercise is maintained (Fig. 1). It has been suggested that an altered respiratory pattern with increased respiratory rate at a similar tidal volume resulting in a greater anatomic dead space ventilation may be responsible for the increase in ventilation/carbon dioxide production slope in patients (9). Work in our department (21) has demonstrated that in normal subjects a change in respiratory pattern does not change the ventilation/carbon dioxide production slope.

The three patterns of response in patients with heart failure have not previously been described. In Group 1 patients, (who demonstrate a near normal curve), the mechanisms of the response may be similar to those in the normal subjects, with an initial decrease in ventilation/carbon dioxide production ratio due to a reduction in dead space. In Group 2 and 3 patients, ventilation/carbon dioxide production ratio increases markedly at the end of exercise. Although there is likely to be a continuous spectrum of ventilation/carbon dioxide production ratio responses during exercise, the increase in the ratio appears to be correlated with the severity of heart failure (Fig. 2).

**Control of ventilation in heart failure.** Current thinking is that increased ventilation in heart failure is due to a ventilation-perfusion mismatch caused by an increase in dead space (. 3). Although direct examination of the effects of ventilation-perfusion mismatch has not proved possible, the cardinal sign of such mismatching is an increase in the alveolar-arterial oxygen difference (22). Although some investigators (5) have identified a widening in alveolar–arterial oxygen difference in heart failure on exercise, others (13) have reported it to be unchanged. Changes in ventilation-perfusion relation during exercise are suggested by changes in ventilation/carbon dioxide production ratio in association with unchanged blood gases, but other explanations for the increased ventilation are possible.

We have observed an increase in ventilation/carbon dioxide production ratio in subsets of patients with severe heart failure. At peak exercise in heart failure, some studies (3,13) have reported a decrease in arterial carbon dioxide and a reduction, or no change, in dead space ventilation (13). In those patients whose blood gas tensions we were able to study, results were similar to those observed by Rajfer et al. (13), with a decrease in physiologic dead space during exercise, even in patients in Group 3, in whom the ventilation/carbon dioxide production ratio increased from the outset of exercise.

It thus seems that ventilation and carbon dioxide production are uncoupled at peak exercise, with carbon dioxide excretion following ventilation passively at a rate determined by ventilation and the dead space ratio. Ventilation may be driven by noncarbon dioxide stimuli, such as a muscle ergoreflex (23), central command (24) or potassium (25,26) and other noncarbon dioxide, non-pH metabolic factors. It may be that the extent to which a noncarbon dioxide factor drives ventilation is a mechanism of the excessive breathlessness in heart failure.

**Conclusions.** The description of different patterns of ventilation/carbon dioxide production ratio relations has implications both for the understanding of the control of breathing and for the use of the ventilation/carbon dioxide production ratio slope as a measure of the severity of chronic heart failure (8). Although plots of the ventilation/carbon dioxide production ratio have high linear correlation coefficients, they are not necessarily related in a cause and effect manner or in a strictly linear fashion. We have shown that the ventilation/carbon dioxide production ratio changes throughout exercise and that the pattern of this change may indicate altered control of ventilation during exercise. The increase in both ventilation and carbon dioxide production should not persuade us that carbon dioxide production is the only determinant of ventilation during exercise in chronic heart failure or that the slope of a "best fit" linear regression

line between ventilation and carbon dioxide production ratio is an adequate description of that relation.

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